RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-23 were originally filed with the application and were pending at the time of the Action. Claims 13 and 19-23 were withdrawn from consideration as directed to a non-elected invention. Claims 2 and 4 are currently amended and claims 24-26 newly added herein. No new matter has been added. Claims 1-12, 14-18, and 24-26 are submitted herein for reconsideration.

B. Rejections Under 35 U.S.C. §112 - Indefiniteness

The Action rejects claims 2-4 under 35 U.S.C. §112 second paragraph for being indefinite. Applicants have amended claims 2 and 4, thereby rendering the rejection moot. Removal of the rejection is thus respectfully requested.

C. Rejections Under 35 U.S.C. §102(e)

The Action rejects claims 1-4 and 9-11 as being anticipated by Heim *et al.* (U.S. Patent Application Publication No. 2003/0188345A1, filed June 28, 2001). Specifically, the Action states that Heim *et al.* disclose use of a plant cell non-lethal negative selectable marker (*codA*) in vector backbone DNA for combined positive/negative selection. The Action also states that Applicants disclose use of the same *codA* gene, thus Heim *et al.* disclose all elements of Applicants' invention. Applicants respectfully traverse.

Heim *et al.* do not anticipate Applicants claims because Heim *et al.* do not disclose a plant expression cassette comprising ***a plant cell non-lethal negative selectable marker gene*** linked to a vector backbone DNA, as the current claims require. A claim is anticipated only if

each and every element set forth in the claim is found expressly or inherently in the prior art. M.P.E.P. §2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Applicants' claim 1 recites:

> A DNA plasmid comprising a T-DNA comprising an Agrobacterium Ti plasmid first border region linked to at least one transgene linked to an Agrobacterium Ti plasmid second border region, and located in the DNA plasmid outside of the T-DNA is a plant expression cassette comprising a plant cell ***non-lethal negative selectable marker gene*** linked to a vector backbone DNA.

(emphasis added). While Applicants disclose *codA* and its use in the Specification, Applicants' claims do not read on *codA* or its use. In fact, Applicants' Specification clearly distinguishes over the use of a conditional lethal marker such as *codA*, or any other conditional lethal marker. For example, in the Background of the Invention section of the specification, it is explained that fungal or bacterial cytosine deaminase (*codA*) will convert 5-fluorocytosine to the toxic compound 5-fluorouracil and can be used as a negative selectable marker. Specification, p.3 ll. 13-20. However, *codA* is identified as a ***conditional lethal gene***. *Id.* It is stated that, when using conditional lethal markers, "exogenous substrates must be added in order to provide the toxic product that is lethal to the cell containing the backbone DNA." *Id.* at p. 3 ll. 27-28. In contrast, Applicants invention involves non-lethal negative selectable marker genes.

The Specification also describes *codA* in reference to FIG. 10, which is a DNA construct with the *codA* coding sequence contained in the vector backbone DNA. The figure description explains that *codA* is a conditional lethal selectable marker, and that callus tissue transformed with *codA* that is transferred to media containing 5-fluorocytosine ***will be killed***. *Id.* at p.30 ll. 10-16. Therefore, *codA* is not a plant cell non-lethal negative selectable marker gene as required by the claims. Thus, Heim *et al.* do not anticipate Applicant's claims, and removal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

D. Rejections Under 35 U.S.C. §103

The Action rejects claims 5-8, 12 and 14-18 as rendered obvious by Heim *et al.* (U.S. Patent Application Publication No. 2003/0188345A1, filed June 28, 2001), in view of Lange *et al.* (U.S. Patent No. 5,939,539) and Ebinuma *et al.* 1997 (*Proc. Natl. Acad. Sc*i USA 94:2117-2121). Specifically, the Action states that Heim *et al.* disclose use of a plant cell non-lethal negative selectable marker (*codA*) in vector backbone DNA for combined positive/negative selection, Lange *et al.* teach a plant hormone degredative/modifying gene as a selectable marker, and Ebinuma *et al.* teach use of the isopentenyl transferase gene (*ipt*) as a selectable marker, thus it would have been *prima facie* obvious for one skill in the art to modify the teachings of Heim *et al.* with those of Lange *et al.* and Ebinuma *et al.* Applicants respectfully traverse.

Applicants' initially note that the claims are not rendered obvious by Heim *et al.* in view of Lange *et al.* and Ebinuma *et al.* because all elements of the claims have not been shown to be found in the art. As explained above, Heim *et al.* do not teach a plant cell non-lethal negative selectable marker gene. Similarly, Lange *et al.* do not teach that the plant hormone degredative/modifying gene (giberellin 20-oxidase) referred to can be used as a non-lethal negative selectable marker. Lange *et al.* disclose in the Summary of the Invention of their Specification "a DNA sequence which encodes a polypeptide exhibiting GA 20-oxidase activity." col.1 ll. 42-44. Beginning at column 17 line 53 and continuing to column 18 line 34, Lange *et al.* describe several uses for their invention for embodiments that both reduce and increase expression of the GA 20 oxidase gene. All of these uses relate to improving agronomic, horticultural, or plant breeding characteristics. However, Lange *et al.* does not teach use of their invention as a non-lethal negative selectable marker.

Ebinuma *et al.* disclose the use of the *ipt* gene as a selectable marker, but only as a positive marker used in a very narrowly specialized selection system. Ebinuma *et al.* is directed to a chimeric *ipt* gene that is entirely inserted into the transposable element *Ac*. Abstract. Ebinuma *et al.* use *ipt* as a positive marker, thus selection is ***for*** expression of the gene as indicating positive transformation. p.2119, col. 2. 1st ¶. Ebinuma *et al.* then rely on the transposon *Ac*'s innate characteristic of randomly moving around a genome to identify transformed culture lines that have lost *ipt* activity some six months after the original transformation event. *Id.* Thus, Ebinuma *et al.* do not teach the use of *ipt* as a non-lethal negative selectable marker gene, as found in Applicants' claims.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. M.P.E.P. § 2143.03; *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In light of the foregoing, no combination of Heim *et al.* with Lange *et al.* and/or Ebinuma *et al.* renders Applicants claims obvious because all limitations of Applicants' claims are not taught or suggested by the cited references.

Further, Applicants claims are patentable over the cited references because the claimed invention yields surprising and unexpected beneficial results relative to the prior art. See M.P.E.P. § 2144.08. In particular, the Specification explains in EXAMPLE 3 that the addition of the non-lethal selectable marker in the vector backbone had the unexpected effect of limiting the number of transgenic plants regenerated that have the backbone DNA, stating:

> Surprisingly, the non-lethal negative selectable marker genes, *ipt* and crtB, provide expectional [sic] reduction in the occurrence of transgenic plants with Ec.oriV DNA. Only five percent of the eight-three plants transformed with pMON75182 contained the Ec.oriV DNA, and only eight percent of the sixty-one plants transformed with pMON75181.

p.35 ll. 24-28. That is, the presence of the non-lethal negative selectable marker genes had the surprising effect of inhibiting regeneration of transgenic plants that contained the backbone sequences even before any screening for such plants took place. This represents a significant advance because substantial efforts are needed to regenerate and screen transgenic plants. This is underscored when taking into account that production of a single given transgene insertion event having a desired expression profile suitable for commercial development may require selection from among hundreds or thousands of different events.

The foregoing benefit is recited in the Detailed Description section of the specification, where it is stated that crtB "is particularly useful for the production of carotenoid pigments and ***in the present invention to reduce plant cell regeneration***." p.12 ll. 16-19 (emphasis added). The Specification also explains that these characteristics have a clear benefit, stating that:

> These results demonstrate the substantial benefit conferred by the DNA plasmids of the present invention by reducing the occurrence of vector backbone. Nearly half of the plants transformed with the conventional DNA plasmid configuration (pMON42066) will be discarded. Of the plants transformed with the DNA plasmids (pMON75182, pMON75181) of the present invention, less than ten percent would be discarded.

p.35 line 29-p. 36 line 2.

Thus, Applicants' claimed invention yields the unexpected, beneficial property of substantially increasing the percentage of transformed plants without vector backbone DNA after a transformation event, without the need for exogenous substrates as required for conditional lethal markers, and without dependence upon another DNA integrating element such as *Ac*.

In addition, the Specification explains that the addition of the non-lethal selectable marker in the vector backbone had the unexpected effect of increasing the percentage of single-copy transformants. As the Specification states:

> The non-lethal selectable marker gene (*ipt*, pMON75182) plasmid shows that the average copy number of the twenty-seven plants assayed is 1.2 and surprisingly, eight-five percent of the transgenic plants are single copy. This result shows the value of the plasmids of the present invention for reducing transgene copy number.

p.37 ll. 4-8.

Similarly, substantially more plants transformed with pMON73565 (crtB+ construct) and pMON67936 (crtB+ construct) had low copy number and were backbone free compared to plants transformed with constructs without the non-lethal selectable marker gene in the backbone. p.38 ll. 3-25. To compare, if the conditional lethal gene *codA* is inserted in the vector backbone, or no gene is inserted in the vector backbone, less than half of the transformants are single-copy. p.36 line 18- p.37 line 3. The importance of the presence of a single transgene copy is disclosed in the specification, for example, at p.36 ll. 6-10. Presence of multiple transgene copies can interfere with transgene expression by causing homology-based transgene silencing. This can also complicate efforts to obtain regulatory approval or introgress transgenes into suitable plant varieties for use by farmers. Thus, the Specification clearly provides evidence that Applicants claimed invention yields unexpected results, affirmatively demonstrating the non-obviousness of the claims. See M.P.E.P. § 2144.08.

In light of all the above, Applicants respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

D. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (512) 536-3085 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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